October 18, 2018

Office of Audit Risk and Compliance

RE: Reporting the findings and responses from the internal OARC audit for REMIT study

Dear OARC team:

The purpose of this letter is to report our responses to the findings of an internal audit conducted by the Duke Office of Audit, Risk and Compliance on the REMIT study, PI: Wei Jiang. The relevant study information is listed below.

DUHS IRB #: Pro00009555 and Pro00014033

DUHS PI: Wei Jiang, MD

I. Summary:

The OARC office conducted an audit of this study in June and July of 2018 and the report was received by the study team on September 10th 2018 and September 12th 2018. Twenty-five subject charts and the regulatory binders were reviewed. A point by point discussion and explanation of the findings and corrective action plan is discussed below.

Please note that the CRU management, Research Practice Manager- Alifia J. Hasan along with Director of Research operations – Terry L. Ainsworth will conduct a thorough review of eligibility status of all subjects randomized in the study. This comprehensive review is expected to be completed by the end of calendar year.

As per the RCA's recommendations, we will also submit the following documentation to the IRB for review:

1. As noted in the findings below, the abbreviated SCID was used for the majority of subjects but an IRB approval was not sought before using that interview in the study. As required by RCA, we are going to submit the abbreviated SCID for REMIT for IRB approval.
2. The missing consent for subject 064-000: We will report the missing consent for participant 064-000, who was not randomized because of no MSIMI, to the IRB and we will generate a NTF indicating the original consent could not be found and the incident was reported to the IRB.

Please find in the table below the responses of the study team to the various findings and non-compliance issues noted during the OARC audit of the studies Pro00009555 and Pro00014033.

Please feel free to contact the study team or the CRU management team, should any questions arise.

Thank you,

Sincerely,

Wei Jiang, MD

Observation	Summary Results	Corrective Recommendations	Study team's response/Corrective Action
Eligibility	16% of subjects reviewed were ineligible per protocol inclusion/exclusion criteria. • 44% of subjects reviewed were missing documentation required to confirm eligibility. • 24% of subjects reviewed, all toward the end of the study, were screened using additional "safety criteria" that were stricter than protocol-approved criteria. These criteria were never used to screen subjects enrolled through the first three years nor were they ever formally incorporated into the protocol. It is unclear if subjects enrolled in the first portion of the trial were at greater risk because they were not screened or enrolled using this "safety criteria."	• Provide to the IRB any missing information required to confirm eligibility for the specific subjects in question and file all additional documentation in the individual subject files. • Provide to the IRB an explanation for "safety criteria" development and use. Detail the range of patients screened using this criteria. Clarify if subjects enrolled prior to implementing the "safety criteria" were at greater risk.	The RCA made a number of observations regarding participant eligibility. We will respond to each in turn. Our CRU team will confirm eligibility of randomized subjects by reviewing all study files and medical records. We will place missing document in study files. Timeline for completion is by the end of the calendar year. In response to the RCA identified non-compliance to REMIT protocol exclusion criteria # 5, (i.e., subjects are ineligible if they are "unable to perform exercise testing.") and the protocol exclusion criteria # 4, (i.e. subjects are ineligible if they are "unable to withdrawal from anti-anginal medications during ischemic assessment phase"), We thoroughly reviewed the entire REMIT study population (N=307, identifying 17 participants who did not perform the exercise stress testing and 30 REMIT participants who did not withdraw from beta blockers before the baseline mental stress testing. While these participants met these exclusion criteria when recruited, we acknowledge that they were not able to comply with these criteria during REMIT baseline screening and we missed asking for single subject exceptions or seeking IRBs approval to amend the criteria in those cases. REMIT participants originally provided study consent with the ability and intention of completing exercise stress testing, but were unable to do so on the day of the testing because of various reasons, which are documented in the patient files (See below for list of reasons). In these cases, the PI thought it appropriate from a participant safety perspective to not complete exercise stress testing. Reschedule for only exercise testing would add more burden on these participants, being constrained by the study resource of the CDU laboratory, and not meet the purpose the study. Not having exercise stress testing had no impact the data integrity of REMIT study for the primary goal of the study, which was to evaluate the effects of escitalopram versus placebo on MSIMI. These patients were still eligible for randomization if they tested positive for MSIMI.

			REMIT participants also originally provided study consent with the ability and intention of withdrawing from beta blockers 24 – 72 hours before stress testing. Several contacts were made to remind the participants. Not every participant (N = 30) was compliant with the beta blocker withhold. Reasons for not withholding beta blockers before the baseline mental stress testing included: cardiologist concerns that some participants blood pressure might be too elevated due to withdrawal; some refused to withhold for reasons due to thinking their blood pressure might be too high; several forgot to withhold, and some participants did not provide reasons for not being compliant. There were 19 participants whose beta blocker withdrawal information were recorded as missing. Of these 19 participants, 5 withheld the beta blocker but either could not specify the duration or only withheld for their morning doses on the day of stress testing. There were no data on beta blocker withholding status for the rest of the 14 participants. The PI elected to have patients who could not be compliant with beta blocker withholding to complete the stress testing rather than rescheduling them as that would have created more burden for the participants, the research staff, and the CDU. Withholding beta blockers up to 5 half-lives was to permit heart rate to respond to exercise stress testing and had little or no effects on mental stress testing responses which are well known not to be characterized by large increases in heart rate. As mentioned, completion of exercise testing was not the primary focus of the study. Thus, we believe that including patients who did not withhold their beta blocker medications had no impact on the primary study goal and did not impact the REMIT data integrity. The RCA also noted concerns about MSIMI assessment as it relates to eligibility. Mental stress testing has not been a routine clinical evaluation. Therefore, we had no knowledge regarding whether or not a potential participant would have had MSIMI prior to the REMIT baseline screening test. MSIMI was the primary inclusion criteria for the REMIT intervention. Electrocardiography, per previous research experience, was insensitive to MSIMI. Therefore we would only learn whether a

			participant had developed MSIMI during the baseline screening from the co-investigating cardiologists who completed their review of the echocardiographic images obtained during his/her mental stress testing. The average window of REMIT team having the MSIMI report from these cardiologists was one week. Baseline echocardiographic images obtained from participants who were randomized to drug or placebo were re-reviewed and re-scored for wall motion abnormalities after the end point (6-week drug intervention) evaluation. This was per protocol and recommended by experts to ascertain high quality of echocardiographic analysis (Detail can be found from Appendix A). Driven by the nature of the imaging technology, having different scores from initial reading was highly likely, as the RCA pointed out that participant (220-078) whose increase in wall motion abnormalities to mental stress during the first read of the echocardiographic data was deemed to not have wall motion abnormalities during the second read. Our surveillance revealed that this reclassification occurred in five of the 112 participants who complete the intervention trial. Such a difference was anticipated according to the intra- and inter reliability of the readers and had little effect on the primary results of the REMIT study that were presented in our publication (Jiang et al JAMA 2013) which demonstrated a significant effect for escitalopram versus placebo to reduce the rate of MSIMI. All echocardiography data (i.e., wall motion scores and left ventricular ejection fraction [LVEF]) are stored electronically on our share drive and the Duke Echocardiography Laboratory Database (DELD) which maintains a comprehensive digital archive of all clinically performed echocardiograms linked to a searchable reporting database. As noted by the RCA, there are some missing LVEF scores. That is because some echocardiographic images were not clear enough to be accurately scored for that variable. This is a phenomenon that occurs in all studies of MSIMI. Failure to obtain LVEF scores was not an exclusion criteria for this study. We only used the dual reads for the primary goal of the intervention assessment.

			The RCA asked if the appearance of the Safety Criteria checklist in later REMIT files marked a change in inclusion/exclusion criteria from those used in the beginning of the trial. Subjects enrolled prior to this checklist being used were not at increased risk for adverse events, nor had any difference in complying with inclusion and exclusion criteria. A new CRC who joined the REMIT team developed this internal worksheet for the purpose of documenting CRC's workflow and this worksheet was not part of the IRB approved protocol. The criteria were not changed. Previous CRCs used different techniques to achieve the same goal. Our CRU team is independently evaluating the eligibility of randomized patients. The timeline for completion is by the end of the calendar year. It should be noted that the PI of the study, Wei Jiang, MD, reviewed patient records and source documents to determine subject eligibility prior to randomization.
Data Quality	Data quality issues were observed in 100% of subject files reviewed. • Poor documentation practices were observed throughout the trial making it difficult to assess the accuracy of data transposed from the original source.	Provide to the IRB a list of subjects for whom stenosis percentages were changed with accompanying source documentation and reasons supporting the changes. File copies of the source documentation supporting the changes in the subject files. • Provide an explanation for discrepancies between data in the Access database and data on forms. Clarify if changes were made directly in the database. • Reconcile all REMIT subject files. All research materials (data and sources) pertaining to the same subject should be organized in one file, for example: Structured Clinical Interview for the Diagnostic	The RCA noted concerns about data quality. We will respond to those in turn. The change of coronary artery stenosis scores noted in the CRF was due to some research staff members entering pre-intracoronary procedure scores into the CRF instead of post-intracoronary procedure scores. These errors were discovered via team data quality examination. The study staff then corrected the scores in the CRF and in the access database accordingly. The source documentation supporting these changes can be found in the participant's file folders. We will place a Note to File (NTF) in the patients' files to document these changes. Most of the research materials (data and sources) pertaining to the same participant are now organized in one file. All echocardiography images, wall motion scores and LVEF scores are stored in the Duke Echocardiography Laboratory Database (DELD). The DELD maintains a comprehensive digital archive of all clinically performed echocardiograms linked to a searchable reporting database. Our collaborators, Eric Velazquez, MD and Zainab Samad, MD provided us with an electronic version of the wall motion and left ventricular

	○ For many subjects, data was generated during treatment, but recorded on forms version-dated after subjects completed treatment. It is unclear if data was transcribed from earlier form versions not found in subject files or where original data was housed in the interim months or years. ○ Paper data did not consistently match the electronic Access database. The PI and statistician confirmed the database was used for publication. It is unclear if changes were made directly in the database or how corrections on paper forms were read by the Access scanner. ○ Multiple sets of forms were used throughout the trial with no audit trail to explain when newer versions should be used. ○ Forms were not designed to capture	and Statistical Manual of Mental Disorders version 4 (SCIDs), echocardiogram (ECHO), electrocardiogram (ECG), submitted data. If space does not allow for this, notes to files (NTFs) explaining where related sources can be located should be included in subject primary files. Wherever possible or appropriate, headers should be completed, and sticky notes removed and replaced with appropriate NTFs, memos, or initialed and dated corrections on submitted data.	ejection fraction scores, which are stored on a shared drive (S:\Sadhart\REMIT\REMIT Database\EF and Wall Motion). Per recommendation of Dr. Geeta Swamy we have printed the final REMIT echocardiographic reports of the 25 REMIT participants the RCA audited We adopted the CRFs templates from DCRI and they included non-protocol variable (HBA1C, troponin and other laboratory measures) which were not used in our analysis. Collection of these values at baseline was done from previous medical records that were part of their standard of clinical care and not part of the REMIT protocol.

	dates data was recorded or by whom. o Corrections were not lined out, initialed, explained or, in some cases, substantiated by source. The percentages of coronary artery stenosis on baseline forms were changed for 52% of subjects reviewed, and forms either missed sources to justify the changes and/or contradicted sources in subject files.		
Specific Protocol Noncompliance	92% of subjects reviewed had study visits and procedures missed and/or not performed per protocol. • There were no left ventricular ejection fractions (LVEF) or wall motion score index (WMSI) values during the mental stress test rest periods for most of the audited subjects. These procedures are represented in the protocol as a direct	• Provide to the IRB a response explaining why LVEF and WMSI were not consistently measured during the rest period after each mental stress test. Describe how this is reflected or qualified in published data. • Submit the abbreviated SCID for IRB approval.	In REMIT, the resting period that was referenced for MSIMI and exercise induced myocardial ischemia was the resting period prior to any stress testing. The resting periods between stress tasks in REMIT study were actually the **recovery** periods. We initially attempted to collect echocardiographic images during these recovery periods because those recovery phases could have been potentially valuable as they would yield feature of recovery. But data from the recovery were not necessary for addressing the specific aims of the REMIT project. Collecting so many images in a short time period placed significant burden on the sonographer in the form of muscle fatigue or even injury. Weighing the benefit versus harm, we eliminated these echocardiographic data during these recovery (or resting) periods between stress tasks after obtaining them from the first several participants. This action did not affect the data integrity and ability to address the specific aims of the REMIT study.

	measure of the primary study objective. • Some protocol-mandated office visits were performed by phone. • Mailing drug was not explicitly approved by the IRB, was not explicitly allowed per protocol, and there was no shipping documentation on record. • Protocol deviations were not tracked. • Known serious issues, including subject drug lost in the mail and repository blood samples lost for three subjects, were never reported to the IRB. • 35 of 100 SCID subject evaluations were not completed (a required baseline assessment that could affect eligibility). IRB requests to monitor subsequent SCID administration do not appear to have occurred. The abbreviated SCID		The REMIT study PI, Dr. Wei Jiang, discovered in early October 2010 via CRF surveillance that the SCID had been conducted inconsistently on some REMIT participants. We reported the issue to the Duke IRB on the timely fashion, and the IRB's letter stating that no further action was needed is filed in the REMIT regulatory binder. As required by RCA, we are going to submit the abbreviated SCID for REMIT for IRB approval.

	used for the majority of subjects represents a deviation and was never IRB-approved.		
Consents	12.7% of informed consent forms (ICFs) reviewed had at least one issue, including one missing ICF, two ICFs without the Person Obtaining Consent (POC) signature, four ICFs where the POC signatures were illegible and could not be compared to the DOA log, 10 signed but incorrect versions, and one where the informed consent process was not carried out appropriately.	• Report the missing consent for subject 064-000 to the IRB. Generate a NTF indicating the original consent could not be found and the incident was reported to the IRB. • Attempt to obtain signatures from anyone still employed at Duke for the REMIT DOA log. Generate a NTF naming all study personnel for whom signatures cannot be obtained.	We will report the missing consent for participant 064-000 to the IRB who was not randomized because of no MSIMI, and we generate a NTF indicating the original consent could not be found and the incident was reported to the IRB. We will attempt to obtain signatures from anyone still employed at Duke for the REMIT DOA log. We generated a NTF naming all study personnel for whom signatures could not be obtained.
Review (CR) Lapse/Subjects Not Re-consented	• REMIT repository trial approval lapsed for eight months. The IRB required the 34 subjects enrolled during the lapse to be re-consented but RCA could not find evidence that this occurred.	• Consult the IRB if it is permissible to use these subject samples or whether existing samples should be destroyed. • If the samples have already been analyzed, work with the IRB to determine if collaborators should be notified of the lapsed approval and	The 34 participants enrolled in the REMIT Repository during the lapse signed the IRB approved letter on 12/11/2008 serving as the repository re-consent, developed under the guidance of the Duke IRB. We have now placed these signed letters in CRFs of these participants accordingly. We have the approval documentation supporting it.

		failure to notify patients, and advised to destroy samples. • Consult the IRB to determine if subjects should be notified of the lapsed approval and re-consented.	
Safety Review Not Performed	• The IRB mandated a safety review of the first 20 patients before the study opened. RCA did not find evidence that this was performed.	• Provide additional documentation including all IRB correspondence and directives regarding the safety review. Clarify if the request was made as part of the IRB initial review and approval. • If the safety review was completed, provide a copy of documentation. If the review was not performed, generate a NTF indicating the review was not performed.	The REMIT team received the Duke IRB approval of the REMIT study on August 2007. During the IRB review and finalization phase, we received the request from Dr. John Harrelson, the IRB Chair who reviewed the REMIT study, to submit a mental stress testing safety report to the IRB after the first 20 participants were tested. The REMIT team submitted the first IRB renewal on 06/20/2008 and first 22 of randomized patients were part of continuing review application. Possibly there was verbal communication about using continuing review as a safety review, however we are unable any documentation supporting this. There had not been safety concerns, nor any study related adverse events.
Drug Accountability Issues	There is explicit documentation that 10 of 25 subjects reviewed (40%) were mailed study drug. Another five subjects reviewed (20%) took medication regularly even though they missed visits where medication was dispensed. Mailing drug was not explicitly approved by the IRB, was not explicitly allowed per protocol and no	• Report lost drug to the IRB. • Provide details on how drug reconciliation and destruction was carried out; include who was responsible for performing pill counts and who was responsible for completing medication count forms. Detail where medication was expected to be stored and describe how unused medication was destroyed.	The REMIT protocol nor IRB had no prohibition from mailing the study drug to the REMIT participant. REMIT study drug was dispensed by the Duke Investigation Drug Services (IDS) to a study coordinator who then gave the drug to the participant in person or via mail. The REMIT study coordinator collected the drug bottles containing unused medication upon the return of the study participants. Drug reconciliation was conducted by study coordinators who performed pill counts and completed pill count forms, which are stored in the patients' files. Unused medication was stored in their offices until time of drug destruction. Drug destruction was carried out by the Duke IDS in accordance with their policy.

	shipping documentation is on record. • One drug calendar used by the subjects reviewed was never approved by the IRB. • One subject's medication was lost in the mail and the subject was sent an additional order. This was not reported to the IRB. There is no documentation indicating how returned drug was stored or destroyed.	.	There was one participant (105-031) whose drug bottle got lost during the mailing. Duke IDS dispensed a replacement for the participant who received safely. We will report the lost drug to the IRB.
Data and Safety Monitoring Board (DSMB) Documentation	• Protocol mandates that the DSMB evaluate, approve and make recommendations regarding subject safety, progress toward recruitment goals, data quality, treatment plan adherence, participant retention/attrition rates, and any necessary modifications or discontinuation of the study. Minutes were not consistently recorded to document what was reviewed, only very brief approval letters.	• File in the regulatory binders all additional documentation provided by the external DSMB and all materials and/or minutes generated before or after the REMIT DSMB meetings. • Generate a NTF explaining that permission to continue enrollment was granted verbally at the June 2009 DSMB meeting and the study team continued enrollment based on that.	The DSMB for the REMIT study provided verbal feedback. However, we acknowledge that this feedback should have also been given in a formal letter from the DSMB chair, Kirkwood Adams MD, per the REMIT DSMB charter. Dr. Kirkwood Adams, the Chair of REMIT DSMB has recently provided a written note via e-mail to confirm that the REMIT DSMB granted permission for REMIT study to continue participant recruitment and testing following the last DSMB meeting in January 2011. We will file all the documentation in the regulatory binder. We will generate a NTF explaining that permission to continue enrollment was granted verbally at the June 2009 DSMB meeting and the study team continued enrollment based on that verbal permission. .

	• The approval letter for the June 2009 meeting was issued February 12, 2010; 55 subjects were consented in that period. • Per protocol, DSMB meetings/approvals must occur annually. Meeting materials prepared for January 2011 were found, but no records that meeting took place were located. Subject enrollment continued through August 2011.		
Regulatory Binders	• Electronic and paper binders were incomplete per GCP guidelines. The study team did not have documentation for the initial IRB approval, many study amendment approvals, many approved materials, and study personnel change approvals. • The REMIT Repository trial did not have its own binder and there was no DOA log, nor was there formal confirmation of whom the PI delegated all trial-specific responsibilities to or	• Perform complete reconciliation of the REMIT and REMIT Repository regulatory binders. • Documents housed within the "Regulatory Binder" and "REMIT Audit" files should be consolidated into one electronic regulatory binder that includes electronic copies of everything in the paper binders. The paper binder should be archived except for documents requiring a wet-ink signature. • If missing or incomplete documents in appendix E are found, file in the electronic binder.	We acknowledge the deficiencies in our regulatory binders and we will take the following steps to correct them. We have retrieved several REMIT DOA updates from the IRB paper-host and will perform a complete reconciliation of the REMIT and REMIT Repository regulatory binders. Documents will be housed within the "Regulatory Binder" and "REMIT Audit" files will be consolidated into one electronic regulatory binder that includes electronic copies of everything in the paper binders. The paper binder will be archived except for documents requiring a wet-ink signature. We will generate NTFs for curricula vitae (CVs), licenses, Collaborative Institutional Training Initiative (CITI) trainings and signatures that cannot be obtained for anyone listed on the DOA or in the eIRB. We will file a NTF explaining any discrepancies between the DOA log and eIRB.

	particular staff responsibilities involved.	• Generate NTFs for curricula vitae (CVs), licenses, Collaborative Institutional Training Initiative (CITI) trainings and signatures that cannot be obtained for anyone listed on the DOA or in the eIRB. • Resolve date discrepancies between eIRB and the DOA log. Anyone listed on one document but not the other should now be added.	
Research Data Security Plan (RDSP)	• The RDSP was not created prior to the May 2018 QA review and the existing one is inaccurate. An accurate RDSP ensures that data is stored securely and that auditors can validate actual data storage against a written plan.	• Revise the REMIT RDSP and include information regarding paper source document worksheets used as scanned data forms. • Specify in the RDSP how access to the electronic database is limited and controlled. • Delete information about who needs to be present during testing.	REMIT did not have a RDSP because the Duke RDSP requirement occurred in 2014, and REMIT had completed participant testing in 2012. A REMIT RDSP was developed in May of 2018. (See Appendix B) as suggested.
Violations of Duke Social Security Number (SSN) Usage Policy	RCA found multiple policy violations including SSNs on health release forms, 28 Accounts Payable Check Request Forms and Excel spreadsheets of patients contacted about study participation.	• Follow recommendations of the OARC Privacy unit assessment to be performed subsequent to the RCA review.	We will remove any SSNs as we find them during the process of cleaning up the study files.

These are Items 12-15 in the Full Report of the Duke Audit for REMIT		
RCA Identified Problems	REMIT Recommendation	REMIT Team Responses
12) DUKE EMPLOYEE ENROLLED WITHOUT REQUIRED IRB APPROVAL; RECRUITMENT OF STUDENTS, EMPLOYEES, FRIENDS, AND FAMILY MEMBERS AS RESEARCH PARTICIPANTS NOT FOLLOWED Subject 220-078 was a Duke University employee consented on October 1, 2009. There was no IRB approval that allowed employees to participate in the REMIT trial as required by the DUHS' Human Research Protection Program (HRPP) policy "Recruitment of Students, Employees, Friends, and Family Members as Research Participants". The current version of the policy can be referenced on the DUHS IRB website; the March 14, 2008 version was in place at the time the subject was enrolled.	Please report this incident to the IRB. It is recommended that the PI and current team study team members confirm in writing that they have reviewed the policy cited above as part of the required response.	This particular REMIT participant (220-078) was recruited from cardiology clinical service at Duke, which was the screening population for this study. Our target population was not Duke employees. We recruited coronary heart disease patients from the Duke clinical service, some of whom were Duke employees. We all have reviewed the Duke IRB policy on enrolling employees and will report this incident to the Duke IRB.
13) ADVERSE EVENTS NOT REPORTED CORRECTLY In the follow-up form completed for patient 302-100, a note indicates that a cardiac cath was done on October 29th, 2010 after patient had pneumonia. The dates the subject had pneumonia were not reported on adverse event forms, and it's unclear when the pneumonia occurred. The subject was randomized on October 22nd, 2010 and completed week 6/visit 8 assessments on December 09, 2010. Pneumonia was not reported while the subject was being treated,	Investigate if and how subject 302-100 had pneumonia while on trial and amend adverse event forms and/or file a SAE report accordingly. Amend subject 342-112's adverse event reporting to include nausea.	According to the REMIT protocol, SAEs (serious and/or severe adverse events) were required to be reported to Duke IRB. Non reportable adverse events were not required to be reported to the IRB. The events experienced by REMIT participants (302-100) and (342-112) did not meet definition of SAE. The patient (302-100) reported that he had walking pneumonia, but did not seek medical assistance for his condition. We deemed the event to not be serious and not to be study related and

although the cath was done during treatment. It should be clarified when the subject had pneumonia, and a Serious Adverse Event (SAE) reported as necessary. Subject 342-112 reported nausea as recorded in the coordinator's notes, but this was not captured on the AE form.		felt it was not necessary to report this to the IRB. We reported to the IRB at the next continuing review that events occurred at a rate that we expected.
14) PROTOCOL INCORRECTLY SPECIFIES THAT DR. JAMES JOLLIS WILL PERFORMED ALL ECHOCARDIOGRAMS The currently approved protocol specifies that Dr. James Jollis perform all ECHOs for study subjects in his laboratory. For the great majority of study subjects, Dr. Jollis had no involvement, and thus, there are hundreds of unnecessary protocol deviations when ECHOs were performed by any other study member. Per Dr. Jiang, Dr. Jollis was not able to comply with the protocol, and other cardiologists were then used. Dr. Jollis' compliance issues were not documented in any trial records reviewed by RCA. Per IRB records, he was removed from key personnel on June 29, 2009, but the protocol was never amended to remove reference to him.	It is recommended that a response detailing Dr. Jollis' non-compliance be provided. It is recommended that the protocol be amended to remove reference to Dr. Jollis.	Dr. Jollis was never non-compliant with the study protocol; he simply did not have the available effort to devote to the study. Therefore, we added additional cardiologists to the study who had documented expertise in echocardiography. Although we removed Dr. Jollis as key personnel, we failed to remove his name from the study protocol. We apologize to the IRB for this oversight. It is important to note that the change in study cardiologists did not increase risk to the participants or threaten data quality.
15) LOST SAMPLES FOR THREE REPOSITORY SUBJECTS Correspondence in the REMIT repository regulatory binder indicated that three tubes of blood were lost for a repository subject. No documentation that this was reported to the IRB could be located.	Please report the three lost tubes of blood to the IRB for the repository subject.	We will report that the repository blood tubes for three participants were lost to the Duke IRB.

Appendix A: Reasons for patients not completing exercise stress testing in the REMIT study	
Patient Number	Reason
20004	Patient could not walk very well.
21000	Patient reported he had a "bad knee", but was still able to exercise. Unfortunately, patient's knee pain worsened close to the testing time and he had knee surgery 4 days after the REMIT baseline testing.
46016	Patient walked with cane and preferred not to walk on the treadmill.
102029	Hx of aortic dissection. Echo cardiologist did not want him to complete the exercise testing.
180051	Aortic aneurysm; Echo cardiologist did not want patient to complete the exercise stress testing.
190000	Blood pressure too high after mental stress testing (SBP = 233). Exercise stress testing canceled due to safety concerns.
196000	Blood pressure too high after mental stress testing (SBP = 238). Exercise stress testing canceled due to safety concerns.
236081	Patient walked with cane and preferred not to walk on the treadmill.
246000	Patient weighed 419 pounds, which is beyond the weight bearing capacity of the treadmill.
253000	Was not able to perform exercise stress testing on that day due to schedule constraint of the participant.
268093	Patient was unable to walk well. This was only apparent on day of testing.
284095	Patient had peripheral artery disease and did not want to perform exercise stress testing on the day of testing.
291000	Left ankle fracture on May 4th. Consented on August 6th with the intent of undergoing the exercise test. Did not do however during the testing day of August 19, 2010. Patient did not have MSIMI.
356000	Suspected to having plantar fasciitis and was unable to perform exercise stress testing on that day due to foot pain.
377121	Reported arm pain due to IV and did not want to perform exercise stress testing.
384000	Leg and knee pain the day of testing.
393000	Patient had prosthetic below the knee and was in pain from walking from the garage so based on his pain level the exercise was not done.

Appendix B: Research Data and Security Plan for REMIT Study

Explain how you will ensure that the subject's privacy will be protected:

Study records that identify the subject will be kept confidential as required by law. Subjects are consented and interviewed by research staff during normal business hours in a private office to ensure privacy. Each subject is assigned a screening ID# which is used on all questionnaires. All subject testing is conducted in Clinic 2K of Duke South where subject privacy is protected. The subject undergoes an EKG and heart rate monitoring, catheter insertion for 2 blood draws, an echocardiogram with 3 mental stress tests, and a physical stress test.

Describe how research data will be stored and secured to ensure confidentiality:

Each subject is assigned a screening ID# which is used on standardized and health questionnaires. Data collected on these are copied on to teleforms and then scanned into an Access database. Reimbursement forms containing subject name, address and SS# are kept in a locked filing cabinet in a private office. All subject data including informed consent documents, standardized and health questionnaires, medical information, teleforms, etc. are also kept in filing cabinets in a locked medical records office. Data are also stored electronically as an Access database and SAS datasets. These datasets are located on S: drive at S:\Sadhart\REMIT\REMIT Database. Access to this location is provided by Mike Campbell in Duke Psychiatry, with the permission of Wei Jiang, MD, the PI of the study. Only members of the team involved with data collection, data management, and data analysis will have access to these data.